IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

SEPRACOR INC.,	:	
	:	
Plaintiff,	:	
	:	C.A. No. 06 113
v.	:	
	:	
DEY, L.P. and	:	
DEY, INC.,	:	
	:	
Defendants.	:	

COMPLAINT FOR PATENT INFRINGEMENT

Plaintiff, Sepracor Inc. ("Sepracor"), for its Complaint against Defendants Dey, L.P. and Dey, Inc. hereby alleges as follows:

THE PARTIES

1. Sepracor is a corporation organized under the laws of Delaware, having its principal place of business at 84 Waterford Drive, Marlborough, MA 01752.

2. Dey, L.P. is a limited partnership organized under the laws of Delaware, having its principal place of business at 2751 Napa Valley Corporate Drive, Napa, California. Dey, L.P.'s registered office in Delaware is located at 1209 Orange Street, Wilmington, Delaware, 19801 and Dey, L.P.'s registered agent for service of process in Delaware is The Corporation Trust Company, 1209 Orange Street, Wilmington, Delaware 19801.

3. Dey, Inc. is a corporation organized under the laws of Delaware, having its principal place of business at 2751 Napa Valley Corporate Drive, Napa, California. Dey, Inc.'s registered office in Delaware is located at 1209 Orange Street, Wilmington, Delaware 19801 and Dey, Inc.'s registered agent for service of process in Delaware is The Corporation Trust Company, 1209 Orange Street, Wilmington, Delaware 19801.

4. Dey, Inc. is the general partner of Dey, L.P. and, as such, Dey, Inc. is liable for the obligations of Dey, L.P.

NATURE OF ACTION

5. This is an action against Dey, L.P. and Dey, Inc. for patent infringement arising under the Patent Laws of the United States, 35 U.S.C. § 100 *et seq.*, and more particularly 35 U.S.C. §§ 271(e)(2) and 281. The act of infringement relates to, *inter alia*, Dey, L.P.'s filing of an Abbreviated New Drug Application ("ANDA") with the United States Food and Drug Administration ("FDA") for approval of copies of certain of Sepracor's XOPENEX® (levalbuterol hydrochloride) inhalation solutions prior to the expiration of various United States Patents owned by Sepracor.

JURISDICTION AND VENUE

6. This Court has subject matter jurisdiction over this action under 28 U.S.C. §§ 1331 and 1338(a).

7. This Court has personal jurisdiction over Dey, L.P. because Dey, L.P. is a Delaware limited partnership with a registered office in Delaware and because Dey, L.P. has designated an agent in Delaware for service of process.

8. This Court has personal jurisdiction over Dey, Inc. because Dey, Inc. is a Delaware corporation with a registered office in Delaware and/or because Dey, Inc. has designated an agent in Delaware for service of process.

9. Venue is proper in this judicial district pursuant to 28 U.S.C. §§ 1391(b), (c) and 1400(b).

PATENTS IN SUIT

10. United States Patent 5,362,755 ("the '755 patent") entitled, "Method for Treating Asthma Using Optically Pure (R)-Albuterol" was duly and legally issued by the United States Patent and Trademark Office on November 8, 1994. Sepracor is and has been the owner of the '755 patent. A true and correct copy of the '755 patent is attached hereto as Exhibit A.

11. United States Patent 5,547,994 ("the '994 patent") entitled, "Method for Treating Asthma Using Optically Pure R(-) Albuterol" was duly and legally issued by the United States Patent and Trademark Office on August 20, 1996. Sepracor is and has been the owner of the '994 patent. A true and correct copy of the '994 patent is attached hereto as Exhibit B.

12. United States Patent 5,760,090 ("the '090 patent") entitled, "Method for Treating Asthma Using Optically Pure R(-) Albuterol" was duly and legally issued by the United States Patent and Trademark Office on June 2, 1998. Sepracor is and has been the owner of the '090 patent. A true and correct copy of the '090 patent is attached hereto as Exhibit C.

13. United States Patent 5,844,002 ("the '002 patent") entitled, "Method for Inducing Bronchodilation Using Optically Pure R(-) Albuterol" was duly and legally issued by the United States Patent and Trademark Office on December 1, 1998. Sepracor is and has been the owner of the '002 patent. A true and correct copy of the '002 patent is hereto as Exhibit D.

14. United States Patent 6,083,993 ("the '993 patent") entitled, "Method for Treating Bronchospasm Using Optically Pure R(-) Albuterol" was duly and legally issued by the United States Patent and Trademark Office on July 4, 2000. Sepracor is and has been the owner of the '993 patent. A true and correct copy of the '993 patent is attached hereto as Exhibit E.

15. Sepracor is the current holder of approved New Drug Application ("NDA") No. 20-837 for XOPENEX® (levalbuterol hydrochloride) inhalation solutions.

ACTS GIVING RISE TO THIS ACTION

16. On information and belief, Dey, L.P. filed its ANDA No. 77-800, allegedly under the provisions of 21 U.S.C. § 355(j), with the FDA in order to obtain approval to engage in the commercial manufacture, use and/or sale of copies of certain XOPENEX® (levalbuterol hydrochloride) inhalation solutions ("Dey's Levalbuterol Inhalation Solutions") before the expiration of Sepracor's '755, '994, '090, '002, and '993 patents (collectively "Sepracor Patents"), which collectively cover Sepracor's XOPENEX® (levalbuterol hydrochloride) inhalation solutions and the FDA approved method of use thereof.

17. In a letter dated January 9, 2006, Dey, L.P. notified Sepracor that it filed its ANDA No. 77-800 seeking approval to engage in the commercial manufacture, use and/or sale of Dey's Levalbuterol Inhalation Solutions and further notifying Sepracor that Dey, L.P. had filed a patent certification pursuant to section 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 355(j)(2)(A)(vii)(IV), directed to the Sepracor Patents.

18. Specifically, in its letter of January 9, 2006, Dey, L.P. stated that it filed its ANDA No. 77-800 to obtain approval from the FDA to "manufacture and sell" Dey's Levalbuterol Inhalation Solutions before expiration of the Sepracor Patents, each of which is listed in the Patent and Exclusivity Information Addendum of FDA's publication, *Approved Drug Products with Therapeutic Equivalence Evaluations* (commonly known as "the Orange Book").

19. In its letter of January 9, 2006, Dey, L.P. further stated generally that its ANDA No. 77-800 contained a certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV).

20. As part of its letter of January 9, 2006, Dey, L.P. asserted more specific purported grounds on which Dey asserts that the Sepracor Patents are either invalid and/or not infringed. Dey, L.P.'s letter asserts no specific grounds for unenforceability of the Sepracor Patents.

COUNT I - INFRINGEMENT OF THE SEPRACOR PATENTS

21. Sepracor incorporates by reference each of the averments of paragraphs 1 through 20 as though fully set forth.

22. Under 35 U.S.C. § 271(e)(2)(A), Dey, L.P.'s submission to the FDA of ANDA No. 77-800 to obtain approval for the commercial manufacture, use and/or sale of Dey's Levalbuterol Inhalation Solutions in the United States before the expiration date of the Sepracor Patents constitutes an act of infringement of one or more claims of each of the Sepracor Patents.

23. Upon FDA approval of Dey, L.P.'s ANDA No. 77-800, Dey will infringe one or more claims of each of the Sepracor Patents by making, offering to sell, selling and/or importing Dey's Levalbuterol Inhalation Solutions in the United States, and/or by actively inducing and/or contributing to infringement by others (collectively "infringe," "infringement," or "infringed"), unless this Court orders that the effective date of any FDA approval of Dey, L.P.'s ANDA shall be no earlier than the expiration date of the Sepracor Patents.

24. Dey, L.P. has actual notice of each of the Sepracor Patents and, upon information and belief, was aware that the filing of its ANDA No. 77-800 and certification with respect to the Sepracor Patents constituted an act of infringement of one or more claims of the Sepracor Patents.

25. On information and belief, Dey, L.P.'s statement of the factual and legal basis for its opinion regarding the validity of the Sepracor Patents is devoid of an objective good faith basis in either the facts or the law.

26. On information and belief, in filing its ANDA No. 77-800 to obtain approval to engage in the commercial manufacture, use and/or sale of Dey's Levalbuterol Inhalation Solutions before the expiration of the Sepracor Patents, Dey, L.P.'s infringement of the Sepracor Patents is, has been and continues to be willful and deliberate.

27. This action was brought before the expiration of forty-five (45) days from the date of receipt by Sepracor of Dey, L.P.'s letter of January 9, 2006.

28. Sepracor will be substantially and irreparably harmed and damaged by Dey, L.P.'s and Dey, Inc.'s infringement if not enjoined.

29. Sepracor has no adequate remedy at law.

30. This case is an exceptional one and Sepracor is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

PRAYER FOR RELIEF

WHEREFORE, Sepracor prays for judgment as follows:

(A) A judgment declaring that Dey, L.P. and Dey, Inc. have infringed and that Dey, L.P.'s and Dey, Inc.'s making, using, selling, offering to sell and/or importing of Dey's Levalbuterol Inhalation Solutions will infringe one or more claims of each of the Sepracor Patents;

(B) A judgment declaring that the effective date of any approval of Dey's ANDA No. 77-800 under Section 505(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355(j)) for Dey's Levalbuterol Inhalation Solutions must be no earlier than the expiration date of the last to expire of the infringed Sepracor Patents.

(C) A permanent injunction enjoining Dey, L.P. and Dey, Inc., their officers, agents, partners, attorneys and employees and anyone acting in concert with them, from making, using,

selling, offering to sell, and/or importing Dey's Levalbuterol Inhalation Solutions until after the expiration of the last to expire of the infringed Sepracor Patents.

(D) A judgment that Dey, L.P.'s and Dey, Inc.'s infringement of the Sepracor Patents was and is willful and that Sepracor is entitled to its reasonable attorneys' fees pursuant to 35 U.S.C. § 285.

(E) A judgment awarding Sepracor costs and expenses in this action.

(F) Such other and further relief as the Court deems just and equitable.

Respectfully submitted,

BUCHANAN INGERSOLL PC

Date: February 22, 2006

By: _____

David E. Wilks (Del. Bar #2793)
The Nemours Building
1007 North Orange Street, Suite 1110
Wilmington, DE 19801
Telephone: (302) 428-5550
Facsimile: (302) 428-3996
wilksde@bipc.com
Attorneys for Plaintiff
SEPRACOR INC.

OF COUNSEL
Jack M. Stover
Jayson R. Wolfgang
BUCHANAN INGERSOLL PC
One South Market Square
213 Market Street, 3rd Floor
Harrisburg, PA 17101-2121

Todd R. Walters
Susan M. Dadio
BUCHANAN INGERSOLL PC
1737 King Street, Suite 500
Alexandria, VA 22314-2727

Exhibit A

(U.S. Patent No. 5,362,755)

US005362755A

United States Patent [19]

Barberich et al.

[11] Patent Number: 5,362,755

[45] Date of Patent: Nov. 8, 1994

[54] METHOD FOR TREATING ASTHMA USING OPTICALLY PURE (R)-ALBUTEROL

[75] Inventors: Timothy J. Barberich, Concord; James W. Young, Still River, both of Mass.

[73] Assignee: Sepracor, Inc., Marlborough, Mass.

[21] Appl. No.: 163,581

[22] Filed: Dec. 7, 1993

Related U.S. Application Data

[63] Continuation of Ser. No. 896,725, Jun. 9, 1992, abandoned, which is a continuation of Ser. No. 461,262, Jan. 5, 1990, abandoned.

[51] Int. Cl.[5] A61K 31/135

[52] U.S. Cl. 514/649; 514/826

[58] Field of Search 514/649, 826

[56] References Cited

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Primary Examiner—Raymond J. Henley, III

Attorney, Agent, or Firm—Heslin & Rothenberg

[57] ABSTRACT

The optically pure R(−) isomer of albuterol, which is substantially free of the S(+) isomer, is a potent bronchodilator for relieving the symptoms associated with asthma in individuals. A method is disclosed utilizing the optically pure R(−) isomer of albuterol for treating asthma while minimizing the side effects associated with chronic administration of racemic albuterol.

7 Claims, No Drawings

METHOD FOR TREATING ASTHMA USING OPTICALLY PURE (R)-ALBUTEROL

This application is a continuation of application Ser. No. 07/896,725 filed Jun. 9, 1992 now abandoned which is a continuation of copending application Ser. No. 07/461,262 filed on Jan. 5, 1990 now abandoned.

DESCRIPTION

1. Background

Albuterol is a drug belonging to the general class of beta-adrenergic compounds. The prime action of beta-adrenergic drugs is to stimulate adenyl cyclase, the enzyme which catalyzes the formation of cyclic-3',5'-adenosine monophosphate (AMP) from adenosine triphosphate (ATP). The cyclic AMP formed mediates the cellular responses. Albuterol acts selectively on beta$_2$-adrenergic receptors to relax smooth muscle tissue, for example, in the bronchial system. Albuterol is most commonly used to treat bronchial spasms associated with asthma and is the active component in well-known commercial bronchodilators such as Proventil and Ventolin.

The form in which albuterol is presently used is a racemic mixture. That is, it is a mixture of optical isomers, called enantiomers. Enantiomers are structurally identical compounds which differ only in that one isomer is a mirror image of the other and the mirror images cannot be superimposed. This phenomenon is known as chirality. Most biological molecules exist as enantiomers and exhibit chirality. Although structurally identical, enantiomers can have profoundly different effects in biological systems: one enantiomer may have a specific biological activity while the other enantiomer has no biological activity at all, or may have an entirely different form of biological activity.

SUMMARY OF THE INVENTION

The present invention relates to a method of treating bronchial disorders, such as asthma, in an individual, by administering to the individual an amount of optically pure R(−) albuterol which is active in bronchial tissue sufficient to reduce bronchial spasms associated with asthma while minimizing side effects associated with albuterol. The method is particularly useful in treating asthma while reducing side effects, such as central nervous system stimulatory effects and cardiac arrythmia. In these applications, it is important to have a composition which is a potent broncho-dilator and which does not exhibit the adverse side effects of many beta-adrenergic drugs. A composition containing the pure R(−) isomer of albuterol is particularly useful for this application because this isomer exhibits these desired characteristics. The present method provides a safe, effective method for treating asthma while reducing undesirable side effects, for example, tremor, nervousness, shakiness, dizziness and increased appetite, and particularly, cardiac arrythmia, typically associated with beta-adrenergic drugs. In children, side effects such as excitement, nervousness and hyperkinesia are reduced when the pure isomer is administered. In addition to the above, at certain levels racemic albuterol can cause teratogenic effects, which are believed to be associated with the S(+) isomer. Administering the pure isomer reduces the teratogenic potential which is associated with the S(+) isomer of albuterol.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relies on the bronchodilation activity of the R(−) enantiomer of albuterol to provide relief from bronchial disorders, while simultaneously reducing undesirable side effects, for example, central nervous system stimulatory effects and cardiac disorders, commonly experienced by albuterol users. In the present method, the optically pure R(−) isomer of albuterol, which is substantially free of the S(+) enantiomer, is administered alone, or in combination with one or more other drug(s) in adjunctive treatment, to an individual in whom asthma relief (e.g., relief from bronchial spasms, shortness of breath) is desired. The optically pure R(−) isomer of albuterol as used herein refers to the levorotatory optically pure isomer of α^1[(-tert-butylamino) methyl]-4-hydroxy-m-xylene-α, α'-diol, and to any biologically acceptable salt or ester thereof. The terms "optically pure" or "substantially free of the S(+) enantiomer" as used herein means that the composition contains at least 90% by weight of the R(−) isomer of albuterol and 10% by weight or less of the S(+) isomer. Optically pure albuterol is readily obtainable by methods known to those of skill in the art, for example, by synthesis from an optically pure intermediate.

In the present method, the R(−) isomer of albuterol is administered to an individual who has asthma. For example, R(−) albuterol is administered to an individual after onset of asthma to reduce breathing difficulty resulting from asthma. In another embodiment, optically pure R(−) albuterol is administered propbylactically, that is, before the bronchiospasm begins in an asthma attack, to prevent its occurrence or to reduce the extent to which it occurs.

In the present method, R(−) albuterol can be administered by inhalation, by subcutaneous or other injection, orally, intravenously, topically, parenterally, transdermally, rectally or via an implanted reservoir containing the drug. The form in which the drug will be administered (e.g., inhalant, powder, tablet, capsule, solution, emulsion) will depend on the route by which it is administered. The quantity of the drug to be administered will be determined on an individual basis, and will be based at least in part on consideration of the individual's size, the severity of the symptoms to be treated and the result sought. In general, quantities of optically pure R(−) albuterol sufficient to reduce the symptoms of asthma will be administered. The actual dosage (quantity administered at a time) and the number of administrations per day will depend on the mode of administration, for example, by inhaler, nebulizer or oral administration. About 30 mcg to about 90 mcg of the optically pure R(−) isomer of albuterol given by inhalation one or more times per day will be adequate in most individuals to produce the desired bronchodilation effect. For oral administration, e.g., tablet or syrup, a dose of about 1 mg to about 8 mg two to four times daily is administered to produce the desired effect.

In the method of the present invention, the optically pure R(−) isomer of albuterol can be administered together with one or more other drug(s). For example, an antiasthmatic drug such as theophylline or terbutaline, or an antihistamine or analgesic such as aspirin, acetaminophen or ibuprofen, can be given with or in close temporal proximity to administration of optically pure, R(−) albuterol. The two (or more) drugs (the

optically pure active isomer of albuterol and another drug) can be administered in one composition or as two separate entities. For example, they can be administered in a single capsule, tablet, powder, or liquid, etc. or as individual compounds. The components included in a particular composition, in addition to optically pure albuterol and another drug or drugs, are determined primarily by the manner in which the composition is to be administered. For example, a composition to be administered in inhalent form can include, in addition to the drug(s), a liquid carrier and/or propellent. A composition to be administered in tablet form can include a filler (e.g., lactose), a binder (e.g., carboxymethyl cellulose, gum arabic, gelatin), an adjuvant, a flavoring agent, a coloring agent and a coating material (e.g., wax or a plasticizer). A composition to be administered in liquid form can include the combination of drugs and, optionally, an emulsifying agent, a flavoring agent and/or a coloring agent.

In general, according to the method of the present invention, the optically pure R(−) isomer of albuterol, alone or in combination with another drug(s), is administered to an individual periodically as necessary to reduce symptoms of asthma.

The present composition and method provide an effective treatment for asthma while minimizing the undesirable side effects associated with albuterol use. These side effects include central nervous system effects, such as tremor, nervousness, shakiness, dizziness and increased appetite, and cardiac effects, such as cardiac arrythmia. In children, side effects, such as excitement, nervousness and hyperkinesia, are reduced when the pure isomer is administered. In addition, teratogenic effects associated with albuterol are believed to reside in the S(+) enantiomer. Thus, administering the pure R(−) isomer may reduce the teratogenic potential associated with albuterol.

Equivalents

Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed in the scope of the following claims.

We claim:

1. A method of treating asthma in an individual with albuterol, while reducing side effects associated with chronic administration of racemic albuterol, comprising chronically administering to the individual a quantity of an optically pure R(−) isomer of albuterol sufficient to result in bronchodilation while simultaneously reducing undesirable side effects, said R isomer being substantially free of its S(+) isomer.

2. A method of claim 1 wherein the amount of the R(−) isomer of albuterol is greater than approximately 90% by weight of total albuterol.

3. A method of claim 2 wherein the amount of the R(−) isomer of albuterol is greater than 99% by weight of total albuterol.

4. A method of claim 1 comprising administering to the individual by inhalation from approximately 30 mcg to approximately 90 mcg of the R(−) isomer of albuterol per dose.

5. A method of claim 1 comprising orally administering to the individual from approximately 1 mg to approximately 8 mg of the R(−) isomer of albuterol two to four times daily.

6. A method of treating asthma in an individual with albuterol, while reducing side effects associated with chronic administration of racemic albuterol, comprising chronically administering to the individual a quantity of an optically pure R(−) isomer of albuterol sufficient to result in bronchodilation while simultaneously reducing undesirable side effects and at least one additional drug selected from the group consisting of bronchodilators, antihistamines and analgesics.

7. A method of claim 6 wherein the analgesic is selected from the group consisting of aspirin, acetaminophen and ibuprofen.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

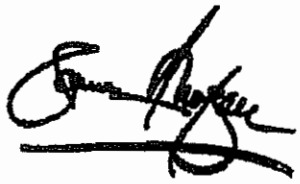
PATENT NO. : 5,362,755
DATED : November 8, 1994
INVENTOR(S) : Barbarich et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 4,
Line 30, delete the word "or" and insert the word -- of --

Signed and Sealed this

Thirtieth Day of September, 2003



JAMES E. ROGAN
Director of the United States Patent and Trademark Office

Exhibit B

(U.S. Patent No. 5,547,994)

US005547994A

United States Patent [19]

Barberich et al.

[11] Patent Number: 5,547,994

[45] Date of Patent: Aug. 20, 1996

[54] **METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(–) ALBUTEROL**

[75] Inventors: Timothy J. Barberich, Concord; James W. Young, Still River, both of Mass.

[73] Assignee: Sepracor, Inc., Marlborough, Mass.

[21] Appl. No.: 335,480

[22] Filed: Nov. 7, 1994

Related U.S. Application Data

[63] Continuation of Ser. No. 163,581, Dec. 7, 1993, Pat. No. 5,362,755, which is a continuation of Ser. No. 896,725, Jun. 9, 1992, abandoned, which is a continuation of Ser. No. 461,262, Jan. 5, 1990, abandoned.

[51] Int. Cl.[6] A61K 31/135

[52] U.S. Cl. 514/649; 514/826

[58] Field of Search 514/649, 826

[56] **References Cited**

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Primary Examiner—Raymond Henley, III
Attorney, Agent, or Firm—Heslin & Rothenberg, P.C.

[57] **ABSTRACT**

The optically pure R(–) isomer of albuterol, which is substantially free of the S(+) isomer, is a potent bronchodilator for relieving the symptoms associated with asthma in individuals. A method is disclosed utilizing the optically pure R(–) isomer of albuterol for treating asthma while minimizing the side effects associated with albuterol.

6 Claims, No Drawings

METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(−) ALBUTEROL

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of application Ser. No. 08/163,581, filed Dec. 7, 1993 and now U.S. Pat. No. 5,362,755, which was a continuation of application Ser. No. 07/896,725, filed Jun. 9, 1992, now abandoned, which was a continuation of application Ser. No. 07/461,262 filed Jan. 5, 1990, now abandoned.

BACKGROUND

Albuterol is a drug belonging to the general class of beta-adrenergic compounds. The prime action of beta-adrenergic drugs is to stimulate adenyl cyclase, the enzyme which catalyzes the formation of cyclic-3',5'-adenosine monophosphate (AMP) from adenosine triphosphate (ATP). The cyclic AMP formed mediates the cellular responses. Albuterol acts selectively on beta$_2$-adrenergic receptors to relax smooth muscle tissue, for example, in the bronchial system. Albuterol is most commonly used to treat bronchial spasms associated with asthma and is the active component in well-known commercial bronchodilators such as Proventil and Ventolin.

The form in which albuterol is presently used is a racemic mixture. That is, it is a mixture of optical isomers, called enantiomers. Enantiomers are structurally identical compounds which differ only in that one isomer is a mirror image of the other and the mirror images cannot be superimposed. This phenomenon is known as chirality. Most biological molecules exist as enantiomers and exhibit chirality. Although structurally identical, enantiomers can have profoundly different effects in biological systems: one enantiomer may have a specific biological activity while the other enantiomer has no biological activity at all, or may have an entirely different form of biological activity.

SUMMARY OF THE INVENTION

The present invention relates to a method of treating bronchial disorders, such as asthma, in an individual, by administering to the individual an amount of optically pure R(−) albuterol which is active in bronchial tissue sufficient to reduce bronchial spasms associated with asthma while minimizing side effects associated with albuterol. The method is particularly useful in treating asthma while reducing side effects, such as central nervous system stimulatory effects and cardiac arrythmia. In these applications, it is important to have a composition which is a potent bronchodilator and which does not exhibit the adverse side effects of many beta-adrenergic drugs. A composition containing the pure R(−) isomer of albuterol is particularly useful for this application because this isomer exhibits these desired characteristics. The present method provides a safe, effective method for treating asthma while reducing undesirable side effects, for example, tremor, nervousness, shakiness, dizziness and increased appetite, and particularly, cardiac arrythmia, typically associated with beta-adrenergic drugs. In children, side effects such as excitement, nervousness and hyperkinesia are reduced when the pure isomer is administered. In addition to the above, at certain levels racemic albuterol can cause teratogenic effects, which are believed to be associated with the S(+) isomer. Administering the pure isomer reduces the teratogenic potential which is associated with the S(+) isomer of albuterol.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relies on the bronchodilation activity of the R(−) enantiomer of albuterol to provide relief from bronchial disorders, while simultaneously reducing undesirable side effects, for example, central nervous system stimulatory effects and cardiac disorders, commonly experienced by albuterol users. In the present method, the optically pure R(−) isomer of albuterol, which is substantially free of the S(+) enantiomer, is administered alone, or in combination with one or more other drug(s) in adjunctive treatment, to an individual in whom asthma relief (e.g., relief from bronchial spasms, shortness of breath) is desired. The optically pure R(−) isomer of albuterol as used herein refers to the levorotatory optically pure isomer of α^1 [(tert-butylamino) methyl] -4-hydroxy-m-xylene-α, α'-diol, and to any biologically acceptable salt or ester thereof. The terms "optically pure" or "substantially free of the S(+) enantiomer" as used herein means that the composition contains at least 90% by weight of the R(−) isomer of albuterol and 10% by weight or less of the S(+) isomer. Optically pure albuterol is readily obtainable by methods known to those of skill in the art, for example, by synthesis from an optically pure intermediate.

In the present method, the R(−) isomer of albuterol is administered to an individual who has asthma. For example, R(−) albuterol is administered to an individual after onset of asthma to reduce breathing difficulty resulting from asthma. In another embodiment, optically pure R(−) albuterol is administered prophylactically, that is, before the bronchiospasm begins in an asthma attack, to prevent its occurrence or to reduce the extent to which it occurs.

In the present method, R(−) albuterol can be administered by inhalation, by subcutaneous or other injection, orally, intravenously, topically, parenterally, transdermally, rectally or via an implanted reservoir containing the drug. The form in which the drug will be administered (e.g., inhalant, powder, tablet, capsule, solution, emulsion) will depend on the route by which it is administered. The quantity of the drug to be administered will be determined on an individual basis, and will be based at least in part on consideration of the individual's size, the severity of the symptoms to be treated and the result sought. In general, quantities of optically pure R(−) albuterol sufficient to reduce the symptoms of asthma will be administered. The actual dosage (quantity administered at a time) and the number of administrations per day will depend on the mode of administration, for example, by inhaler, nebulizer or oral administration. About 30 mcg to about 90 mcg of the optically pure R(−) isomer of albuterol given by inhalation one or more times per day will be adequate in most individuals to produce the desired bronchodilation effect. For oral administration, e.g., tablet or syrup, a dose of about 1 mg to about 8 mg two to four times daily is administered to produce the desired effect.

In the method of the present invention, the optically pure R(−) isomer of albuterol can be administered together with one or more other drug(s). For example, an antiasthmatic drug such as theophylline or terbutaline, or an antihistamine or analgesic such as aspirin, acetaminophen or ibuprofen, can be given with or in close temporal proximity to administration of optically pure, R(−) albuterol. The two (or more) drugs (the optically pure active isomer of albuterol and another drug) can be administered in one composition or as two separate entities. For example, they can be administered in a single capsule, tablet, powder, or liquid, etc. or as individual compounds. The components included in a par-

ticular composition, in addition to optically pure albuterol and another drug or drugs, are determined primarily by the manner in which the composition is to be administered. For example, a composition to be administered in inhalent form can include, in addition to the drug(s), a liquid carrier and/or propellent. A composition to be administered in tablet form can include a filler (e.g., lactose), a binder (e.g., carboxymethyl cellulose, gum arabic, gelatin), an adjuvant, a flavoring agent, a coloring agent and a coating material (e.g., wax or a plasticizer). A composition to be administered in liquid form can include the combination of drugs and, optionally, an emulsifying agent, a flavoring agent and/or a coloring agent.

In general, according to the method of the present invention, the optically pure R(−) isomer of albuterol, alone or in combination with another drug(s), is administered to an individual periodically as necessary to reduce symptoms of asthma.

The present composition and method provide an effective treatment for asthma while minimizing the undesirable side effects associated with albuterol use. These side effects include central nervous system effects, such as tremor, nervousness, shakiness, dizziness and increased appetite, and cardiac effects, such as cardiac arrythmia. In children, side effects, such as excitement, nervousness and hyperkinesia, are reduced when the pure isomer is administered. In addition, teratogenic effects associated with albuterol are believed to reside in the S(+) enantiomer. Thus, administering the pure R(−) isomer may reduce the teratogenic potential associated with albuterol.

EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed in the scope of the following claims.

We claim:

1. A method of treating an acute attack of asthma, while reducing side effects associated with the acute administration of racemic albuterol, comprising administering to an individual suffering from an acute attack of asthma a quantity of an optically pure R(−) isomer of albuterol sufficient to result in bronchodilation while simultaneously reducing undesirable side effects, said R isomer being substantially free of its S(+) isomer.

2. A method of claim 1 wherein the amount of the R(−) isomer of albuterol is greater than approximately 90% by weight.

3. A method of claim 2 wherein the amount of the R(−) isomer of albuterol is greater than 99% by weight.

4. A method of claim 1 comprising administering to the individual by inhalation from approximately 30 mcg to approximately 90 mcg of the R(−) isomer of albuterol per dose.

5. A method of treating an acute attack of asthma, while reducing side effects associated with the acute administration of racemic albuterol, comprising administering to an individual suffering from an acute attack of asthma a quantity of an optically pure R(−) isomer of albuterol sufficient to result in bronchodilation while simultaneously reducing undesirable side effects, and at least one additional drug selected from the group consisting of bronchodilators, antihistamines and analgesics.

6. A method of claim 5 wherein the analgesic is selected from the group consisting of: aspirin, acetaminophen and ibuprofen.

* * * * *

Exhibit C

(U.S. Patent No. 5,760,090)

US005760090A

United States Patent [19]

Barberich et al.

[11] Patent Number: 5,760,090

[45] Date of Patent: *Jun. 2, 1998

[54] METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(–) ALBUTEROL

[75] Inventors: Timothy J. Barberich, Concord; James W. Young, Still River, both of Mass.

[73] Assignee: Sepracor, Inc., Marlborough, Mass.

[*] Notice: The term of this patent shall not extend beyond the expiration date of Pat. No. 5,362,755.

[21] Appl. No.: 691,604

[22] Filed: Aug. 15, 1996

Related U.S. Application Data

[63] Continuation of Ser. No. 335,480, Nov. 7, 1994, Pat. No. 5,547,994, which is a continuation of Ser. No. 163,581, Dec. 7, 1993, Pat. No. 5,362,755, which is a continuation of Ser. No. 896,725, Jun. 9, 1992, abandoned, which is a continuation of Ser. No. 461,262, Jan. 5, 1990, abandoned.

[51] Int. Cl.[6] A61K 31/135

[52] U.S. Cl. 514/649; 514/826

[58] Field of Search 514/649

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Primary Examiner—Raymond Henley, III

Attorney, Agent, or Firm—Heslin & Rothenberg, P.C.

[57] ABSTRACT

The optically pure R(–) isomer of albuterol, which is substantially free of the S(+) isomer, is a potent bronchodilator for relieving the symptoms associated with asthma in individuals. A method is disclosed utilizing the optically pure R(–) isomer of albuterol for treating asthma while minimizing the side effects associated with albuterol.

9 Claims, No Drawings

METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(−) ALBUTEROL

This is a continuation of U.S. application Ser. No. 08/335,480, filed Nov. 7, 1994, now U.S. Pat. No. 5,547,994, which is a continuation of U.S. application Ser. No. 08/163,581 filed Dec. 7, 1993, now U.S. Pat. No. 5,362,755, which is a continuation of U.S. application Ser. No. 07/896,725, filed Jun. 9, 1992, abandoned, which is a continuation of U.S. application Ser. No. 07/461,262, filed Jan. 5, 1990, abandoned.

BACKGROUND

Albuterol is a drug belonging to the general class of beta-adrenergic compounds. The prime action of beta-adrenergic drugs is to stimulate adenyl cyclase, the enzyme which catalyzes the formation of cyclic-3',5'-adenosine monophosphate (AMP) from adenosine triphosphate (ATP). The cyclic AMP formed mediates the cellular responses. Albuterol acts selectively on beta$_2$-adrenergic receptors to relax smooth muscle tissue, for example, in the bronchial system. Albuterol is most commonly used to treat bronchial spasms associated with asthma and is the active component in well-known commercial bronchodilators such as Proventil and Ventolin.

The form in which albuterol is presently used is a racemic mixture. That is, it is a mixture of optical isomers, called enantiomers. Enantiomers are structurally identical compounds which differ only in that one isomer is a mirror image of the other and the mirror images cannot be superimposed. This phenomenon is known as chirality. Most biological molecules exist as enantiomers and exhibit chirality. Although structurally identical, enantiomers can have profoundly different effects in biological systems: one enantiomer may have a specific biological activity while the other enantiomer has no biological activity at all, or may have an entirely different form of biological activity.

SUMMARY OF THE INVENTION

The present invention relates to a method of treating bronchial disorders, such as asthma, in an individual, by administering to the individual an amount of optically pure R(−) albuterol which is active in bronchial tissue sufficient to reduce bronchial spasms associated with asthma while minimizing side effects associated with albuterol. The method is particularly useful in treating asthma while reducing side effects, such as central nervous system stimulatory effects and cardiac arrythmia. In these applications, it is important to have a composition which is a potent bronchodilator and which does not exhibit the adverse side effects of many beta-adrenergic drugs. A composition containing the pure R(−) isomer of albuterol is particularly useful for this application because this isomer exhibits these desired characteristics. The present method provides a safe, effective method for treating asthma while reducing undesirable side effects, for example, tremor, nervousness, shakiness, dizziness and increased appetite, and particularly, cardiac arrythmia, typically associated with beta-adrenergic drugs. In children, side effects such as excitement, nervousness and hyperkinesia are reduced when the pure isomer is administered. In addition to the above, at certain levels racemic albuterol can cause teratogenic effects, which are believed to be associated with the S(+) isomer. Administering the pure isomer reduces the teratogenic potential which is associated with the S(+) isomer of albuterol.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relies on the broncho-dilation activity of the R(−) enantiomer of albuterol to provide relief from

bronchial disorders, while simultaneously reducing undesirable side effects, for example, central nervous system stimulatory effects and cardiac disorders, commonly experienced by albuterol users. In the present method, the optically pure R(−) isomer of albuterol, which is substantially free of the S(+) enantiomer, is administered alone, or in combination with one or more other drug(s) in adjunctive treatment, to an individual in whom asthma relief (e.g., relief from bronchial spasms, shortness of breath) is desired. The optically pure R(−) isomer of albuterol as used herein refers to the levorotatory optically pure isomer of α^1[(tert-butylamino) methyl] -4-hydroxy-m-xylene-α, α-diol, and to any biologically acceptable salt or ester thereof. The terms "optically pure" or "substantially free of the S(+) enantiomer" as used herein means that the composition contains at least 90% by weight of the R(−) isomer of albuterol and 10% by weight or less of the S(+) isomer. Optically pure albuterol is readily obtainable by methods known to those of skill in the art, for example, by synthesis from an optically pure intermediate.

In the present method, the R(−) isomer of albuterol is administered to an individual who has asthma. For example, R(−) albuterol is administered to an individual after onset of asthma to reduce breathing difficulty resulting from asthma. In another embodiment, optically pure R(−) albuterol is administered prophylactically, that is, before the bronchiospasm begins in an asthma attack, to prevent its occurrence or to reduce the extent to which it occurs.

In the present method, R(−) albuterol can be administered by inhalation, by subcutaneous or other injection, orally, intravenously, topically, parenterally, transdermally, rectally or via an implanted reservoir containing the drug. The form in which the drug will be administered (e.g., inhalant, powder, tablet, capsule, solution, emulsion) will depend on the route by which it is administered. The quantity of the drug to be administered will be determined on an individual basis, and will be based at least in part on consideration of the individual's size, the severity of the symptoms to be treated and the result sought. In general, quantities of optically pure R(−) albuterol sufficient to reduce the symptoms of asthma will be administered. The actual dosage (quantity administered at a time) and the number of administrations per day will depend on the mode of administration, for example, by inhaler, nebulizer or oral administration. About 30 mcg to about 90 mcg of the optically pure R(−) isomer of albuterol given by inhalation one or more times per day will be adequate in most individuals to produce the desired bronchodilation effect. For oral administration, e.g., tablet or syrup, a dose of about 1 mg to about 8 mg two to four times daily is administered to produce the desired effect.

In the method of the present invention, the optically pure R(−) isomer of albuterol can be administered together with one or more other drug(s). For example, an antiasthmatic drug such as theophylline or terbutaline, or an antihistamine or analgesic such as aspirin, acetaminophen or ibuprofen, can be given with or in close temporal proximity to administration of optically pure, R(−) albuterol. The two (or more) drugs (the optically pure active isomer of albuterol and another drug) can be administered in one composition or as two separate entities. For example, they can be administered in a single capsule, tablet, powder, or liquid, etc. or as individual compounds. The components included in a particular composition, in addition to optically pure albuterol and another drug or drugs, are determined primarily by the manner in which the composition is to be administered. For example, a composition to be administered in inhalent form can include, in addition to the drug(s), a liquid carrier and/or

propellent. A composition to be administered in tablet form can include a filler (e.g., lactose), a binder (e.g., carboxymethyl cellulose, gum arabic, gelatin), an adjuvant, a flavoring agent, a coloring agent and a coating material (e.g., wax or a plasticizer). A composition to be administered in liquid form can include the combination of drugs and, optionally, an emulsifying agent, a flavoring agent and/or a coloring agent.

In general, according to the method of the present invention, the optically pure R(−) isomer of albuterol, alone or in combination with another drug(s), is administered to an individual periodically as necessary to reduce symptoms of asthma.

The present composition and method provide an effective treatment for asthma while minimizing the undesirable side effects associated with albuterol use. These side effects include central nervous system effects, such as tremor, nervousness, shakiness, dizziness and increased appetite, and cardiac effects, such as cardiac arrythmia. In children, side effects, such as excitement, nervousness and hyperkinesia, are reduced when the pure isomer is administered. In addition, teratogenic effects associated with albuterol are believed to reside in the S(+) enantiomer. Thus, administering the pure R(−) isomer may reduce the teratogenic potential associated with albuterol.

EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed in the scope of the following claims.

We claim:

1. A method of treating asthma, while reducing side effects associated with the administration of racemic albuterol, comprising administering to an individual suffering from asthma a quantity of an optically pure R(−) isomer of albuterol sufficient to result in bronchodilation while simultaneously reducing undesirable side effects, said R isomer being substantially free of its S(+) isomer.

2. A method according to claim 1, wherein the albuterol comprises at least 90% by weight of the R(−) isomer and not more than 10% by weight of the S(+) isomer.

3. A method according to claim 1, wherein the albuterol comprises at least 99% by weight of the R(−) isomer and 1% or less by weight of the S(+) isomer.

4. A method according to claim 1, wherein the optically pure R(−) albuterol is administered by inhalation.

5. A method according to claim 4, wherein the optically pure R(−) albuterol is administered in an amount of about 30 μg to about 90 μg.

6. A method according to claim 1, wherein the optically pure R(−) albuterol is administered orally.

7. A method according to claim 6, wherein the optically pure R(−) albuterol is administered in an amount of about 1 mg to about 8 mg.

8. A method according to claim 6, wherein the optically pure R(−) albuterol is administered as a syrup.

9. A method according to claim 7, wherein the optically pure R(−) albuterol is administered as a syrup.

* * * * *

Exhibit D

(U.S. Patent No. 5,844,002)

US005844002A

United States Patent [19]

Barberich et al.

[11] Patent Number: 5,844,002

[45] Date of Patent: Dec. 1, 1998

[54] **METHOD FOR INDUCING BRONCHODILATION USING OPTICALLY PURE R(-) ALBUTEROL**

[75] Inventors: Timothy J. Barberich, Concord; James W. Young, Still River, both of Mass.

[73] Assignee: Sepracor, Inc., Marlborough, Mass.

[21] Appl. No.: 63,551

[22] Filed: Apr. 21, 1998

Related U.S. Application Data

[63] Continuation of Ser. No. 691,604, Aug. 15, 1996, Pat. No. 5,760,090, which is a continuation of Ser. No. 335,480, Nov. 7, 1994, Pat. No. 5,547,994, which is a continuation of Ser. No. 163,581, Dec. 7, 1993, Pat. No. 5,362,755, which is a continuation of Ser. No. 896,725, Jun. 9, 1992, abandoned, which is a continuation of Ser. No. 461,262, Jan. 5, 1990, abandoned.

[51] Int. Cl.[6] A61K 31/135

[52] U.S. Cl. 514/649; 514/826

[58] Field of Search 514/649, 826

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Hawkins et al. "Relative Potency of (−)–and (±)–Salbutamol on Guinea Pig . . . " *J. Med. Chem.* 16, 856–857 (1973).

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Chapman et al. "Racemic mixtures at root of worsening symptoms? Active enantiomers . . ." *TIPS* 13, 231–232 (1992).

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Primary Examiner—Raymond Henley, III

Attorney, Agent, or Firm—Heslin & Rothenberg, P.C.

[57] ABSTRACT

The optically pure R(−) isomer of albuterol, which is substantially free of the S(+) isomer, is a potent bronchodilator for relieving the symptoms associated with asthma in individuals. A method is disclosed utilizing the optically pure R(−) isomer of albuterol for treating asthma while minimizing the side effects associated with albuterol.

10 Claims, No Drawings

METHOD FOR INDUCING BRONCHODILATION USING OPTICALLY PURE R(−) ALBUTEROL

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of application Ser. No. 08/691,604, filed Aug. 15, 1996, now U.S. Pat. No. 5,760,090, which is a continuation of application Ser. No. 08/335,480, filed Nov. 7, 1994, now U.S. Pat. No. 5,547,994, which is a continuation of application Ser. No. 08/163,581, filed Dec. 7, 1993 now U.S. Pat. No. 5,362,755, which is a continuation of application Ser. No. 07/896,725, filed Jun. 9, 1992 now abandoned, which was a continuation of application Ser. No. 07/461,262, filed Jan. 5, 1990, now abandoned.

BACKGROUND

Albuterol is a drug belonging to the general class of beta-adrenergic compounds. The prime action of beta-adrenergic drugs is to stimulate adenyl cyclase, the enzyme which catalyzes the formation of cyclic-3',5'-adenosine monophosphate (AMP) from adenosine triphosphate (ATP). The cyclic AMP formed mediates the cellular responses. Albuterol acts selectively on beta$_2$-adrenergic receptors to relax smooth muscle tissue, for example, in the bronchial system. Albuterol is most commonly used to treat bronchial spasms associated with asthma and is the active component in well-known commercial bronchodilators such as Proventil and Ventolin.

The form in which albuterol is presently used is a racemic mixture. That is, it is a mixture of optical isomers, called enantiomers. Enantiomers are structurally identical compounds which differ only in that one isomer is a mirror image of the other and the mirror images cannot be superimposed. This phenomenon is known as chirality. Most biological molecules exist as enantiomers and exhibit chirality. Although structurally identical, enantiomers can have profoundly different effects in biological systems: one enantiomer may have a specific biological activity while the other enantiomer has no biological activity at all, or may have an entirely different form of biological activity.

SUMMARY OF THE INVENTION

The present invention relates to a method of treating bronchial disorders, such as asthma, in an individual, by administering to the individual an amount of optically pure R(−) albuterol which is active in bronchial tissue sufficient to reduce bronchial spasms associated with asthma while minimizing side effects associated with albuterol. The method is particularly useful in treating asthma while reducing side effects, such as central nervous system stimulatory effects and cardiac arrythmia. In these applications, it is important to have a composition which is a potent bronchodilator and which does not exhibit the adverse side effects of many beta-adrenergic drugs. A composition containing the pure R(−) isomer of albuterol is particularly useful for this application because this isomer exhibits these desired characteristics. The present method provides a safe, effective method for treating asthma while reducing undesirable side effects, for example, tremor, nervousness, shakiness, dizziness and increased appetite, and particularly, cardiac arrythmia, typically associated with beta-adrenergic drugs. In children, side effects such as excitement, nervousness and hyperkinesia are reduced when the pure isomer is administered. In addition to the above, at certain levels racemic albuterol can cause teratogenic effects, which are believed to be associated with the S(+) isomer. Administering the pure isomer reduces the teratogenic potential which is associated with the S(+) isomer of albuterol.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relies on the broncho-dilation activity of the R(−) enantiomer of albuterol to provide relief from bronchial disorders, while simultaneously reducing undesirable side effects, for example, central nervous system stimulatory effects and cardiac disorders, commonly experienced by albuterol users. In the present method, the optically pure R(−) isomer of albuterol, which is substantially free of the S(+) enantiomer, is administered alone, or in combination with one or more other drug(s) in adjunctive treatment, to an individual in whom asthma relief (e.g., relief from bronchial spasms, shortness of breath) is desired. The optically pure R(−) isomer of albuterol as used herein refers to the levorotatory optically pure isomer of α^2[(tert-butylamino) methyl] -4-hydroxy-m-xylene-α, α'-diol, and to any biologically acceptable salt or ester thereof. The terms "optically pure" or "substantially free of the S(+) enantiomer" as used herein means that the composition contains at least 90% by weight of the R(−) isomer of albuterol and 10% by weight or less of the S(+) isomer. Optically pure albuterol is readily obtainable by methods known to those of skill in the art, for example, by synthesis from an optically pure intermediate.

In the present method, the R(−) isomer of albuterol is administered to an individual who has asthma. For example, R(−) albuterol is administered to an individual after onset of asthma to reduce breathing difficulty resulting from asthma. In another embodiment, optically pure R(−) albuterol is administered prophylactically, that is, before the bronchiospasm begins in an asthma attack, to prevent its occurrence or to reduce the extent to which it occurs.

In the present method, R(−) albuterol can be administered by inhalation, by subcutaneous or other injection, orally, intravenously, topically, parenterally, transdermally, rectally or via an implanted reservoir containing the drug. The form in which the drug will be administered (e.g., inhalant, powder, tablet, capsule, solution, emulsion) will depend on the route by which it is administered. The quantity of the drug to be administered will be determined on an individual basis, and will be based at least in part on consideration of the individual's size, the severity of the symptoms to be treated and the result sought. In general, quantities of optically pure R(−) albuterol sufficient to reduce the symptoms of asthma will be administered. The actual dosage (quantity administered at a time) and the number of administrations per day will depend on the mode of administration, for example, by inhaler, nebulizer or oral administration. About 30 mcg to about 90 mcg of the optically pure R(−) isomer of albuterol given by inhalation one or more times per day will be adequate in most individuals to produce the desired bronchodilation effect. For oral administration, e.g., tablet or syrup, a dose of about 1 mg to about 8 mg two to four times daily is administered to produce the desired effect.

In the method of the present invention, the optically pure R(−) isomer of albuterol can be administered together with one or more other drug(s). For example, an antiasthmatic drug such as theophylline or terbutaline, or an antihistamine or analgesic such as aspirin, acetaminophen or ibuprofen, can be given with or in close temporal proximity to administration of optically pure, R(−) albuterol. The two (or more)

drugs (the optically pure active isomer of albuterol and another drug) can be administered in one composition or as two separate entities. For example, they can be administered in a single capsule, tablet, powder, or liquid, etc. or as individual compounds. The components included in a particular composition, in addition to optically pure albuterol and another drug or drugs, are determined primarily by the manner in which the composition is to be administered. For example, a composition to be administered in inhalent form can include, in addition to the drug(s), a liquid carrier and/or propellent. A composition to be administered in tablet form can include a filler (e.g., lactose), a binder (e.g., carboxymethyl cellulose, gum arabic, gelatin), an adjuvant, a flavoring agent, a coloring agent and a coating material (e.g., wax or a plasticizer). A composition to be administered in liquid form can include the combination of drugs and, optionally, an emulsifying agent, a flavoring agent and/or a coloring agent.

In general, according to the method of the present invention, the optically pure R(−) isomer of albuterol, alone or in combination with another drug(s), is administered to an individual periodically as necessary to reduce symptoms of asthma.

The present composition and method provide an effective treatment for asthma while minimizing the undesirable side effects associated with albuterol use. These side effects include central nervous system effects, such as tremor, nervousness, shakiness, dizziness and increased appetite, and cardiac effects, such as cardiac arrythmia. In children, side effects, such as excitement, nervousness and hyperkinesia, are reduced when the pure isomer is administered. In addition, teratogenic effects associated with albuterol are believed to reside in the S(+) enantiomer. Thus, administering the pure R(−) isomer may reduce the teratogenic potential associated with albuterol.

Equivalents

Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed in the scope of the following claims.

We claim:

1. A method of inducing bronchodilation or providing relief of bronchospasm, comprising administering to an individual a quantity of optically pure R-(−) albuterol sufficient to induce said bronchodilation.

2. A method according to claim 1, wherein the albuterol comprises at least 90% by weight of the R(−) isomer and not more than 10% by weight of the S(+) isomer.

3. A method according to claim 1, wherein the albuterol comprises at least 99% by weight of the R(−) isomer and 1% or less by weight of the S(+) isomer.

4. A method according to claim 1, wherein the optically pure R(−) albuterol is administered by inhalation.

5. A method according to claim 4, wherein the optically pure R(−) albuterol is administered in an amount of about 30 μg to about 90 μg.

6. A method according to claim 1, wherein the optically pure R(−) albuterol is administered orally.

7. A method according to claim 6, wherein the optically pure R(−) albuterol is administered in an amount of about 1 mg to about 8 mg.

8. A method according to claim 6, wherein the optically pure R(−) albuterol is administered as a syrup.

9. A method according to claim 7, wherein the optically pure R(−) albuterol is administered as a syrup.

10. A method of inducing bronchodilation or providing relief of bronchospasm while reducing the concomitant liability of adverse effects associated with racemic albuterol, comprising administering to an individual a quantity of optically pure R-(−) albuterol sufficient to induce said bronchodilation while simultaneously reducing said adverse effects.

* * * * *

Exhibit E

(U.S. Patent No. 6,083,993)

US006083993A

United States Patent [19]

Barberich et al.

[11] Patent Number: 6,083,993

[45] Date of Patent: *Jul. 4, 2000

[54] METHOD FOR TREATING BRONCHOSPASM USING OPTICALLY PURE R(–) ALBUTEROL

[75] Inventors: Timothy J. Barberich, Concord; James W. Young, Still River, both of Mass.

[73] Assignee: Sepracor Inc., Marlborough, Mass.

[*] Notice: This patent is subject to a terminal disclaimer.

[21] Appl. No.: 09/466,107

[22] Filed: Dec. 17, 1999

Related U.S. Application Data

[63] Continuation of application No. 09/200,541, Nov. 25, 1998, which is a continuation of application No. 09/063,551, Apr. 21, 1998, Pat. No. 5,844,002, which is a continuation of application No. 08/691,604, Aug. 15, 1996, Pat. No. 5,760,080, which is a continuation of application No. 08/335,480, Nov. 7, 1994, Pat. No. 5,547,994, which is a continuation of application No. 08/163,581, Dec. 7, 1993, Pat. No. 5,362,755, which is a continuation of application No. 07/896,725, Jun. 9, 1992, abandoned, which is a continuation of application No. 07/461,262, Jan. 5, 1990, abandoned.

[51] Int. Cl.[7] A61K 31/135

[52] U.S. Cl. 514/649

[58] Field of Search 514/649

[56] References Cited

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Primary Examiner—Raymond Henley, III

Attorney, Agent, or Firm—Heslin & Rothenberg, P.C.

[57] ABSTRACT

The optically pure R(–) isomer of albuterol, which is substantially free of the S(+) isomer, is a potent bronchodilator for relieving the symptoms associated with asthma in individuals. A method is disclosed utilizing the optically pure R(–) isomer of albuterol for treating asthma while minimizing the side effects associated with albuterol.

17 Claims, No Drawings

METHOD FOR TREATING BRONCHOSPASM USING OPTICALLY PURE R(−) ALBUTEROL

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of our prior copending application Ser. No. 09/200,541, filed Nov. 25, 1998, which is a continuation of application Ser. No. 09/063,551, filed Apr. 21, 1998, now U.S. Pat. No. 5,844,002, which was a continuation of application Ser. No. 08/691,604, filed Aug. 15, 1996, now U.S. Pat. No. 5,760,090, which was a continuation of application Ser. No. 08/335,480, filed Nov. 7, 1994, now U.S. Pat. No. 5,547,994, which was a continuation of application Ser. No. 08/163,581, filed Dec. 7, 1993, now U.S. Pat. No. 5,362,755, which was a continuation of application Ser. No. 07/896,725, filed Jun. 9, 1992 now abandoned, which was a continuation of application Ser. No. 07/461,262, filed Jan. 5, 1990, now abandoned.

BACKGROUND

Albuterol is a drug belonging to the general class of beta-adrenergic compounds. The prime action of beta-adrenergic drugs is to stimulate adenyl cyclase, the enzyme which catalyzes the formation of cyclic-3',5'-adenosine monophosphate (AMP) from adenosine triphosphate (ATP). The cyclic AMP formed mediates the cellular responses. Albuterol acts selectively on $beta_2$-adrenergic receptors to relax smooth muscle tissue, for example, in the bronchial system. Albuterol is most commonly used to treat bronchial spasms associated with asthma and is the active component in well-known commercial bronchodilators such as Proventil and Ventolin.

The form in which albuterol is presently used is a racemic mixture. That is, it is a mixture of optical isomers, called enantiomers. Enantiomers are structurally identical compounds which differ only in that one isomer is a mirror image of the other and the mirror images cannot be superimposed. This phenomenon is known as chirality. Most biological molecules exist as enantiomers and exhibit chirality. Although structurally identical, enantiomers can have profoundly different effects in biological systems: one enantiomer may have a specific biological activity while the other enantiomer has no biological activity at all, or may have an entirely different form of biological activity.

SUMMARY OF THE INVENTION

The present invention relates to a method of treating bronchial disorders, such as asthma, in an individual, by administering to the individual an amount of optically pure R(−) albuterol which is active in bronchial tissue sufficient to reduce bronchial spasms associated with asthma while minimizing side effects associated with albuterol. The method is particularly useful in treating asthma while reducing side effects, such as central nervous system stimulatory effects and cardiac arrythmia. In these applications, it is important to have a composition which is a potent bronchodilator and which does not exhibit the adverse side effects of many beta-adrenergic drugs. A composition containing the pure R(−) isomer of albuterol is particularly useful for this application because this isomer exhibits these desired characteristics. The present method provides a safe, effective method for treating asthma while reducing undesirable side effects, for example, tremor, nervousness, shakiness, dizziness and increased appetite, and particularly, cardiac arrythmia, typically associated with beta-adrenergic drugs.

In children, side effects such as excitement, nervousness and hyperkinesia are reduced when the pure isomer is administered. In addition to the above, at certain levels racemic albuterol can cause teratogenic effects, which are believed to be associated with the S(+) isomer. Administering the pure isomer reduces the teratogenic potential which is associated with the S(+) isomer of albuterol.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relies on the bronchodilation activity of the R(−) enantiomer of albuterol to provide relief from bronchial disorders, while simultaneously reducing undesirable side effects, for example, central nervous system stimulatory effects and cardiac disorders, commonly experienced by albuterol users. In the present method, the optically pure R(−) isomer of albuterol, which is substantially free of the S(+) enantiomer, is administered alone, or in combination with one or more other drug(s) in adjunctive treatment, to an individual in whom asthma relief (e.g., relief from bronchial spasms, shortness of breath) is desired. The optically pure R(−) isomer of albuterol as used herein refers to the levorotatory optically pure isomer of α^1[(tert-butylamino) methyl]-4-hydroxy-mxylene-α, α'-diol, and to any biologically acceptable salt or ester thereof. The terms "optically pure" or "substantially free of the S(+) enantiomer" as used herein means that the composition contains at least 90% by weight of the R(−) isomer of albuterol and 10% by weight or less of the S(+) isomer. Optically pure albuterol is readily obtainable by methods known to those of skill in the art, for example, by synthesis from an optically pure intermediate.

In the present method, the R(−) isomer of albuterol is administered to an individual who has asthma. For example, R(−) albuterol is administered to an individual after onset of asthma to reduce breathing difficulty resulting from asthma. In another embodiment, optically pure R(−) albuterol is administered prophylactically, that is, before the bronchiospasm begins in an asthma attack, to prevent its occurrence or to reduce the extent to which it occurs.

In the present method, R(−) albuterol can be administered by inhalation, by subcutaneous or other injection, orally, intravenously, topically, parenterally, transdermally, rectally or via an implanted reservoir containing the drug. The form in which the drug will be administered (e.g., inhalant, powder, tablet, capsule, solution, emulsion) will depend on the route by which it is administered. The quantity of the drug to be administered will be determined on an individual basis, and will be based at least in part on consideration of the individual's size, the severity of the symptoms to be treated and the result sought. In general, quantities of optically pure R(−) albuterol sufficient to reduce the symptoms of asthma will be administered. The actual dosage (quantity administered at a time) and the number of administrations per day will depend on the mode of administration, for example, by inhaler, nebulizer or oral administration. About 30 mcg to about 90 mcg of the optically pure R(−) isomer of albuterol given by inhalation one or more times per day will be adequate in most individuals to produce the desired bronchodilation effect. For oral administration, e.g., tablet or syrup, a dose of about 1 mg to about 8 mg two to four times daily is administered to produce the desired effect.

In the method of the present invention, the optically pure R(−) isomer of albuterol can be administered together with one or more other drug(s). For example, an antiasthmatic drug such as theophylline or terbutaline, or an antihistamine

or analgesic such as aspirin, acetaminophen or ibuprofen, can be given with or in close temporal proximity to administration of optically pure, R(−) albuterol. The two (or more) drugs (the optically pure active isomer of albuterol and another drug) can be administered in one composition or as two separate entities. For example, they can be administered in a single capsule, tablet, powder, or liquid, etc. or as individual compounds. The components included in a particular composition, in addition to optically pure albuterol and another drug or drugs, are determined primarily by the manner in which the composition is to be administered. For example, a composition to be administered in inhalent form can include, in addition to the drug(s), a liquid carrier and/or propellent. A composition to be administered in tablet form can include a filler (e.g., lactose), a binder (e.g., carboxymethyl cellulose, gum arabic, gelatin), an adjuvant, a flavoring agent, a coloring agent and a coating material (e.g., wax or a plasticizer). A composition to be administered in liquid form can include the combination of drugs and, optionally, an emulsifying agent, a flavoring agent and/or a coloring agent.

In general, according to the method of the present invention, the optically pure R(−) isomer of albuterol, alone or in combination with another drug(s), is administered to an individual periodically as necessary to reduce symptoms of asthma.

The present composition and method provide an effective treatment for asthma while minimizing the undesirable side effects associated with albuterol use. These side effects include central nervous system effects, such as tremor, nervousness, shakiness, dizziness and increased appetite, and cardiac effects, such as cardiac arrythmia. In children, side effects, such as excitement, nervousness and hyperkinesia, are reduced when the pure isomer is administered. In addition, teratogenic effects associated with albuterol are believed to reside in the S(+) enantiomer. Thus, administering the pure R(−) isomer may reduce the teratogenic potential associated with albuterol.

EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed in the scope of the following claims.

What is claimed is:

1. A method of treating bronchospasm in a patient with reversible obstructive airway disease, comprising administering to said patient a therapeutically effective amount of optically pure R-(−) albuterol.

2. A method according to claim 1, wherein the albuterol comprises at least 90% by weight of the R(−) isomer and not more than 10% by weight of the S(+) isomer.

3. A method according to claim 1, wherein the albuterol comprises at least 99% by weight of the R(−) isomer and 1% or less by weight of the S(+) isomer.

4. A method according to claim 1, wherein the optically pure R(−) albuterol is administered by inhalation.

5. A method according to claim 4, wherein the optically pure R(−) albuterol is administered in an amount of about 30 μg to about 90 μg.

6. A method according to claim 1, wherein the optically pure R(−) albuterol is administered orally.

7. A method according to claim 6, wherein the optically pure R(−) albuterol is administered in an amount of about 1 mg to about 8 mg.

8. A method according to claim 6, wherein the optically pure R(−) albuterol is administered as a tablet, capsule or syrup.

9. A method according to claim 7, wherein the optically pure R(−) albuterol is administered as a syrup.

10. A method of preventing bronchospasm in a patient with reversible obstructive airway disease, comprising administering to said patient a therapeutically effective amount of optically pure R-(−) albuterol.

11. A method according to claim 10, wherein the albuterol comprises at least 90% by weight of the R(−) isomer and not more than 10% by weight of the S(+) isomer.

12. A method according to claim 10, wherein the albuterol comprises at least 99% by weight of the R(−) isomer and 1% or less by weight of the S(+) isomer.

13. A method according to claim 10, wherein the optically pure R(−) albuterol is administered by inhalation.

14. A method according to claim 13, wherein the optically pure R(−) albuterol is administered in an amount of about 30 μg to about 90 μg.

15. A method according to claim 10, wherein the optically pure R(−) albuterol is administered orally.

16. A method according to claim 15, wherein the optically pure R(−) albuterol is administered in an amount of about 1 mg to about 8 mg.

17. A method according to claim 15, wherein the optically pure R(−) albuterol is administered as a tablet, capsule or syrup.

* * * * *

JS 44
(Rev. 12/96)

CIVIL COVER SHEET

06 113

The JS-44 civil cover sheet and the information contained herein neither replace nor supplement the filing and service of pleadings or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. (SEE INSTRUCTIONS ON THE REVERSE OF THE FORM.)

I.(a) PLAINTIFFS
Sepracor Inc.

(b) COUNTY OF RESIDENCE OF FIRST LISTED PLAINTIFF New Castle
(EXCEPT IN U.S. PLAINTIFF CASES)

DEFENDANTS
Dey, LP and Dey, Inc.

COUNTY OF RESIDENCE OF FIRST LISTED DEFENDANT _____
(IN U.S. PLAINTIFF CASES ONLY)

NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF THE TRACT OF LAND INVOLVED.

(c) ATTORNEYS (FIRM NAME, ADDRESS, AND TELEPHONE NUMBER)
David E. Wilks (#2793)
Buchanan Ingersoll PC
1007 North Orange Street, Suite 1110
Wilmington, DE 19802-1236
(302) 428-5500

ATTORNEYS (IF KNOWN)

FILED
FEB 22 PM 5:

II. BASIS OF JURISDICTION (PLACE AN X IN ONE BOX ONLY)

- ☐ 1 U.S. Government Plaintiff
- ☒ 3 Federal Question (U.S. Government Not a Party)
- ☐ 2 U.S. Government Defendant
- ☐ 4 Diversity (Indicate Citizenship of Parties in Item III)

III. CITIZENSHIP OF PRINCIPAL PARTIES (PLACE AN "X" IN ONE BOX FOR PLAINTIFF AND ONE BOX FOR DEFENDANT)
(For Diversity Cases Only)

	PTF	DEF		PTF	DEF
Citizen of This State	☐ 1	☐ 1	Incorporated or Principal Place of Business in This State	☐ 4	☐ 4
Citizen of Another State	☐ 2	☐ 2	Incorporated and Principal Place of Business in Another State	☐ 5	☐ 5
Citizen or Subject of a Foreign Country	☐ 3	☐ 3	Foreign Nation	☐ 6	☐ 6

IV. ORIGIN (PLACE AN X IN ONE BOX ONLY)

☒ 1 Original Proceeding | ☐ Removed from State Court | ☐ 3 Remanded from Appellate Court | ☐ 4 Reinstated or Reopened | ☐ 5 Appeal to District Transferred from another district (specify) | ☐ 6 Multidistrict Litigation | ☐ 7 Judge from Magistrate Judgment

V. NATURE OF SUIT (PLACE AN X IN ONE BOX ONLY)

CONTRACt
- ☐ 110 Insurance
- ☐ 120 Marine
- ☐ 130 Miller Act
- ☐ 140 Negotiable Instrument
- ☐ 150 Recovery of Overpayment & Enforcement of Judgment
- ☐ 151 Medicaro Act
- ☐ 152 Recovery of Defaulted Student Loans (excl. Veterans)
- ☐ 153 Recovery of Ovorpayment of Veteran's Benefits
- ☐ 160 Stockholder's Suits
- ☐ 190 Other Conlrect
- ☐ 195 Contract Product Liability

REAL PROPERTY
- ☐ 210 Land Condemnation
- ☐ 220 Foreclosure
- ☐ 230 Rent Lease & Eject
- ☐ 240 Torts to Land
- ☐ 245 Tort Product Liability
- ☐ 290 All Other Real Property

TORTS

PERSONAL INJURY
- ☐ 310 Airplane
- ☐ 315 Airplane Product Liability
- ☐ 320 Assault, Libel & Slander
- ☐ 330 Federal Employers' Liability
- ☐ 340 Marine
- ☐ 345 Marine Product Liability
- ☐ 350 Motor Vehicle
- ☐ 355 Motor Vehicle Preduct Liability
- ☐ 360 Other Personal Injury

CIVIL RIGHTS
- ☐ 441 Voting
- ☐ 442 Employment
- ☐ 443 Housing/ Accommodations
- ☐ 444 Welfare
- ☐ 440 Other Civil Rights

PERSONAL INJURY
- ☐ 362 Personal Injury - Med. Malpractice
- ☐ 365 Personal Injury - Product Liability
- ☐ 366 Asbestos Personal Injury Preduct Liability

PERSONAL PROPERTY
- ☐ 370 Other Fraud
- ☐ 371 Truth In Lending
- ☐ 380 Other Parsonal Property Damage
- ☐ 385 Property Damago Product Liability

PRISONER PETITIONS
- ☐ 510 Motions to Vacate Sentence Habeas Corpus:
- ☐ 530 General
- ☐ 535 Death Penalty
- ☐ 540 Mandamus & Other
- ☐ 550 Civil Rights
- ☐ 555 Prison Condition

FORFEITURE/PENALTY
- ☐ 610 Agriculture
- ☐ 620 Other Feed & Drug
- ☐ 625 Drug Related Seizure of Property 21 USC 881
- ☐ 630 L iquor Laws
- ☐ 640 R.R. & Truck
- ☐ 650 Airline Regs.
- ☐ 660 Occupational Safety/Health
- ☐ 690 Other

LABOR
- ☐ 710 Fair Labor Standards Act
- ☐ 720 Labor/Mgmt. Relations
- ☐ 730 Labor/Mgmt. Reporting & Disclosure Act
- ☐ 740 Railway Labor Act
- ☐ 790 Other Labor Lit igation
- ☐ 791 Empl. Ret. Inc. Security Act

BANKRUPTCY
- ☐ 422 Appeal 28 USC 158
- ☐ 423 Withdrawal 28 USC 157

PROPERTY RIGHTS
- ☐ 620 Copyrights
- ☒ 630 Patent
- ☐ 640 Trademark

SOCIAL SECURITY
- ☐ 861 HIA (1395ff)
- ☐ 862 Black Lung (923)
- ☐ 863 DIWC/DIWW (405(g))
- ☐ 864 S SID Title XVI
- ☐ 865 RSI (405(g))

FEDERAL TAX SUITS
- ☐ 870 Taxes (U.S. Plaintiff or Defendant)
- ☐ 871 IRS - Third Party 26 USC 7609

OTHER STATUTES
- ☐ 400 State Reappointment
- ☐ 410 Antitrust
- ☐ 430 Banks and Banking
- ☐ 450 Commerce/ICC Rates/etc.
- ☐ 460 Deportetion
- ☐ 470 Ra cketeer Influenced and Corrupt Organizations
- ☐ 610 Selective Service
- ☐ 860 Securities /Commodities/Exchange
- ☐ 875 Customer Challenge 12 USC 3410
- ☐ 891 Agricultural Acts
- ☐ 892 Ecenomic Stabilization Act
- ☐ 893 Environmental Melters
- ☐ 894 Energy Allocation Act
- ☐ 695 Freedom of Information Act
- ☐ 900 Appeal of Fee Determination Under Equal Access to Justice
- ☐ 950 Constitutionality of State Slatutes
- ☐ 890 Other Statutory Actions

VI. CAUSE OF ACTION (CITE THE U.S. CIVIL STATUTE UNDER WHICH YOU ARE FILING AND WRITE A BRIEF STATEMENT OF CAUSE. DO NOT CITE JURISDICTIONAL STATUTES UNLESS DIVERSITY.)

Action for patent infringement under 35 U.S.C. § 100, et seq.

VII. REQUESTED IN COMPLAINT: CHECK IF THIS IS A **CLASS ACTION** ☐ Under F.R.C.P. 23 **DEMAND $**

CHECK YES only if demanded in complaint:
JURY DEMAND: ___ YES _x_ NO

VIII. RELATED CASE(S) (See instructions): **IF ANY** Judge_____ Docket Number ___

DATE February 22, 2006

SIGNATURE OF ATTORNEY OF RECORD David E Wilks

FOR OFFICE USE ONLY

RECEIPT #_____ AMOUNT ____ APPLYING IFP_____ JUDGE _____ MAG. JUDGE _____